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World Workshop on Oral Medicine VII: Biomarkers predicting lymphoma in the salivary glands of patients with Sjögren's syndrome. A systematic review.

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Abstract

Objective: To conduct a systematic review of studies exploring potential biomarkers for development, course and efficacy of treatment of lymphomas in salivary glands of patients with Sjögren's syndrome.

Material and Methods: Eligible studies were identified through a comprehensive search of two databases, i.e. PubMed and EMBASE. Quality of included articles was assessed with the 'Quality In Prognosis Studies' (QUIPS) tool. The 'Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies' (CHARMS) was used to facilitate data extraction.

Results: Fifty-eight studies met the inclusion criteria. Only one study assessed the progression of lymphoma. Moderate risk of bias was detected in 'outcome measurement', 'study participation' and 'study confounding' domains. Parotid gland enlargement, mixed monoclonal cryoglobulins and low C4 levels represented strongest predictors of lymphoma development. The role of histological biomarkers, and specifically germinal centers, remains controversial. Clinical and methodological heterogeneity across studies precluded conduct of a meta-analysis.

Conclusions: Specific biomarkers in combination with clinical manifestations represent potential candidates for advancing precision medicine approaches to lymphoma prediction in patients with Sjögren's syndrome. Current focus has increasingly been on genetic and epigenetic markers as candidate predictors. Predictive accuracy of key biomarker candidates remains to be tested in well-designed prospectively-followed Sjögren's syndrome cohorts.

Introduction

Sjögren's syndrome (SS) is a common rheumatic disease with an estimated prevalence of 61 cases per 100 000 inhabitants in the general population (Qin *et al.*, 2015). SS commonly affects the salivary and lacrimal glands, while the most common symptoms are sensation of dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca) (Vissink *et al.*, 2012). Although exact pathogenic mechanism remains to be elucidated, the minor and major salivary glands are characteristically infiltrated by mononuclear lymphoid cells (Kroese *et al.*, 2013). Enlargement of major salivary glands, especially the parotid and submandibular gland, is also a common phenomenon. This enlargement is usually bilateral, may be non-painful to slightly tender, as well as intermittent to persistent in nature. An estimated 7.5% of patients with SS develop malignant B-cell lymphoma during the course of their disease, 48-75% of which is of the MALT-type (Sutcliffe *et al.*, 1998; Theander *et al.*, 2006).

Translation of precision medicine into mainstream clinical care is being prioritized worldwide and is increasingly being advanced as the future paradigm for more effective medical management. Precision medicine, also coined as P4 medicine by Hood and Friend (2011), who characterized it as being 'predictive', 'preventive', 'personalized' and 'participatory', embraces a systems approach to understanding underlying disease pathophysiology coupled with individually- tailored health care informed by an individual's genes, lifestyle and environment (Hodson, 2016). Advancement of precision medicine has remained largely in the increasingly-active research arena which is rapidly expanding the list of candidate biomarkers and definition of clinical phenotypes, with only a few advances of note in the clinical arena. As a recent example, a high pretreatment number of CD20+ B-cells/mm² was shown to predict the responsiveness of patients with SS to rituximab treatment, therefore contributing to a more personalized treatment approach (Delli *et al.*, 2016).

Since precision medicine approaches to targeting specific molecules in biological pathways continues to successfully make inroads into cancer treatment and improved survival outcomes, research efforts have focused on defining both phenotypic characteristics and molecular signals that underlie emergence of glandular lymphomas that evolve in a subset of at-risk individuals with SS. In order to provide precision medicine to patients with SS, it is also of utmost importance to be able to predict not only the development and course of lymphoma in their salivary glands but also response to treatment. Such knowledge will allow health care providers to closely monitor high-risk SS patients, intervene as early as possible, and administer a targeted personalized treatment protocol. The growing evidence base continues to report on relevant biomarkers that have been extensively studied to date and continue to remain under investigation. In addition, meta-omics research approaches are rapidly expanding the scope of additional biomarkers which, in combination with clinical phenotypes, may be candidates for translation into the clinical arena in the foreseeable future. Therefore, the aim of this study was to conduct a systematic review in order to identify potential predictive biomarkers for development, course and efficacy of treatment of lymphomas in the salivary glands of patients with SS.

Material and methods

a. Literature search strategy

A systematic literature search of two electronic databases (PubMed and EMBASE) was undertaken to identify publications on biomarkers and other phenotypic characteristics associated with identifying risk for lymphoma detected in salivary glands and course of lymphoma in patients with SS. To insure comprehensiveness of the search, manual review of citations of relevant studies was also undertaken to identify additional relevant publications not identified by the search strategy. No language or temporal restrictions were

applied. According to the syntax rules of each database, key words and their combinations were used to identify the studies published prior to June 2018 (Table S1).

b. Study eligibility

Two observers (K.D. and A. Vis.) independently assessed titles and abstracts identified in the initial search. Inclusion criteria were studies examining potential biomarkers predicting lymphoma development or course or efficacy of lymphoma treatment in the salivary glands of patients with SS. Exclusion criteria which applied to title and abstract reviews included: case reports, case series with fewer than five cases, expert opinion publications, letters to the editor, review articles, studies that did not report on potential biomarkers predicting lymphoma development or course or treatment in the salivary glands of patients with SS, and congress abstracts. If the title and abstract provided only limited information, or if eligibility could not be readily discerned, publications then underwent full text assessment. The results of the assessment were compared, and any disagreement was resolved by consensus of the two reviewers.

Full texts of the included titles and abstracts were independently assessed according to the aforementioned criteria by the same observers. Additionally, the 'Quality In Prognosis Studies' (QUIPS) tool was used to assess the risk of bias of the included studies (Hayden *et al.*, 2013). This tool consists of six domains covering 'study participation', 'study attrition', 'prognostic factor measurement', 'outcome measurement', 'study confounding', and 'statistical analysis and reporting'. After each stage of selection, inter-observer agreement was calculated as Cohen's kappa and percentage of agreement. Studies written in a language in which the assessors were not proficient were translated into English by researchers fluent in both that language and English. Data extraction was performed on study and patient characteristics, and on the validity of biomarkers to predict lymphoma development and efficacy of lymphoma treatment in the salivary glands of patients with SS. The 'Checklist for critical Appraisal and data extraction for systematic Reviews of prediction

Modelling Studies' (CHARMS) was used to facilitate data extraction (Moons *et al*, 2014). The reporting of this study complied with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement (Moher *et al.*, 2009).

c. Statistical analysis

Inter-observer agreement applying Cohen's Kappa and absolute agreement was calculated with IBM Statistic9s 23 (SPSS, Chicago, Illinois, USA). Data were tabulated into a Microsoft Excel spreadsheet and simple descriptive analyses were performed (Microsoft Excel 2010, Redmond Washington, USA).

Results

1. Study identification and selection

A total of 1,086 papers was initially identified. Search results were imported into RefWorks (ProQuest LLC, Ann Arbor, Michigan, USA), compiled and duplicates were removed by the software. The remaining papers were further scanned individually to manually remove undetected duplicates. After excluding duplicates, 814 papers were retrieved and underwent title and abstract review (Figure 1). Subsequently, 677 titles and abstracts were excluded (a list of all identified papers and excluded papers not presented in this paper can be requested from the corresponding author). Cohen's Kappa agreement was 0.983 and the absolute agreement was 99.6%. Additional manual review of the literature did not identify any articles meeting inclusion criteria. The full text of 137 studies was then screened. Finally, 58 studies were included for quality assessment (Figure 1). Cohen's Kappa and absolute agreement at this stage was 0.803 and 90.4%, respectively. Manual review of citations of relevant studies did not yield any additional eligible studies.

2. Quality assessment of studies

Low risk of bias was observed in 'prognostic factor measurement', 'study attrition' and 'statistical analysis' (84.5%, 55.3% and 50.0% of the included studies, respectively), while moderate risk of bias was identified in 'outcome measures', 'study participation' and 'study confounding' in 91.4%, 75.9% and 65.5% of the studies, respectively. The percentage of studies with high risk of bias was low, and varied across the different domains between 0-12% of the included studies (Figure 2; Supplementary Table 2).

3. Study characteristics

In the 58 studies that were included for quality assessment, SS was diagnosed according to the American European Consensus Group (AECG) Criteria (Vitali *et al.*, 2002), European Community Study Group (ECSG) Criteria (Vitali *et al.*, 1993), or other criteria in 72%, 16% and 12%, respectively. One study used the recently published 2016 American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) criteria (Shiboski *et al.*, 2017). The source of data of the included studies was from cohort (53%), case-control (30%), registry (10%) or other (i.e., case series or unspecified, 7%) studies. In 44% of the included studies, consecutively enrolled patients were included; in 24.5% of the included studies participants were included only if data of interest were available. In 31.5% of the studies the patients' eligibility and recruitment method was not specified. The majority of the studies (53%) were performed at a single institution, while 32% of the studies had multi-center design with the number of participating centers ranging from 2 to 15.

In total, 1,418 patients with SS and lymphoma were investigated. In 77% of studies lymphomas were explicitly defined as non-Hodgkin lymphoma (NHL). Among these, 70% explicitly defined the NHL as B-type. In 65% of the studies, mucosa associated lymphoma tissue (MALT) type was described. Lymphoma type was not specified in 22% of studies. Follow-up of patients was described in 53% of the studies with reported duration of follow-up

ranging from 1.9 to 46.6 years. In the majority of studies (94%), the approach to lymphoma diagnosis was not specified nor if it was diagnosed with the same method for all patients.

4. Predictive biomarkers

i. Combination of clinical and serological biomarkers

The majority of studies investigated the predictive value of clinical manifestations *in combination with* serological biomarkers. As shown in Table 1 and regarding the various clinical manifestations assessed, the following were more frequently associated with patients with SS who developed lymphoma: presence of parotid gland enlargement, purpura, peripheral nervous system involvement, splenomegaly, lymphadenopathy, Raynaud's phenomenon, fibromyalgia, high EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), clinical ESSDAI (clinESSDAI, i.e., ESSDAI without the biological domain), high/high-intermediate international prognostic index (IPI), bone marrow involvement and low grade fever. These clinical manifestations were typically investigated in combination with serological biomarkers, including presence of neutropenia, cryoglobulinemia, hypergammaglobulinemia, hypocomplementemia, (i.e., low C3 levels and/or low C4 levels), leukocytopenia, anemia, monoclonal gammopathy, thrombocytopenia, anti-Ro/SSA or/and anti-La/SSB, rheumatoid factor (RF) positivity, elevated lactic dehydrogenase (LDH) and CD4+ lymphocytopenia. Table 1 summarizes key findings among studies assessing a combination of clinical and serological biomarkers. Parotid gland enlargement in combination with low C4 levels was found to be predictive of lymphoma development in approximately half of the studies (Fragioudaki *et al.*, 2016; Ioannidis *et al.*, 2002; Ismail *et al.*, 2013; Nocturne *et al.*, 2016; Risselada *et al.*, 2013; Solans-Laqué *et al.*, 2011).

ii. Serological biomarkers

The predictive value of serological biomarkers was the second most popular studied model with 11 studies retrieved. Serological or laboratory measures under consideration as potential candidate biomarkers associated with emergence of lymphoma in salivary glands among patients with SS included: presence of anemia, anti-SSA and/or anti-SSB positivity, cryoglobulinemia, high levels of Fms-like tyrosine kinase 3 ligand, hypergammaglobulinemia, leukopenia, hypocomplementemia, i.e. low C3 levels and/or low C4 levels, and monoclonal gammopathy (Table 2). Hypocomplementemia and/or cryoglobulinemia, were found to be predictive of lymphoma development in all relevant studies (Brito-Zeron *et al.*, 2017, De Vita *et al.*, 2012; Kimman *et al.*, 2018; Martel *et al.*, 2011; Quartuccio *et al.*, 2015; Quartuccio *et al.*, 2014; Ramos-Casals *et al.*, 2005; Ramos-Casals *et al.*, 2008; Retamozo *et al.*, 2016; Tzioufas *et al.*, 1996).

iii. Histological characteristics

One of the most common yet controversial histologic risk factors assessed regarding lymphoma prediction was the presence of germinal centers (GC). Several studies concluded that the presence of GC in diagnostic biopsies was not predictive of MALT lymphoma development in SS patients (Kapsogeorgou *et al.*, 2013; Johnsen *et al.*, 2014; Haacke *et al.*, 2017), while others showed opposite results (Bombardieri *et al.*, 2007; Theander *et al.*, 2011; Sene *et al.*, 2018). Lymphocytic focus score (LFS) ≥ 3 , i.e. ≥ 3 aggregates of 50 or more lymphocytes/4 mm² of glandular tissue, was found to be able to identify SS patients with an increased risk for lymphoma development (Risselada *et al.*, 2014; Risselda *et al.*, 2015; Carrubi *et al.*, 2015). Similarly, elevated FcRL4+ expression (Haacke *et al.*, 2017) and pSTAT-3 expression (Ciccia *et al.*, 2015) were reported in diagnostic biopsies of patients who developed MALT lymphoma, while weak or absent A20 staining was observed in the majority of patients with MALT lymphoma (Johnsen *et al.*, 2016). Sugai *et al.* (1994)

suggested that lymphoma development might be related to suppression of apoptotic death by Bcl-2, while Ussmuller *et al.* (2002) support that myoepithelial sialoadenitis, defined as benign lymphoepithelial lesions, were highly relevant in predicting lymphoma development.

iv. Genetics

Fragkioudaki *et al.* (2017) investigated the prevalence of specific polymorphisms in the methylene tetrahydrofolate reductase (*MTHFR*) gene and observed an increased frequency of c. 677C > T TT genotype and T allele, as well as reduced prevalence of the c. 1298A > C C allele in the subset of patients with SS who did not develop MALT lymphoma compared to controls and patients without NHL. Five single nucleotide polymorphisms (SNPs) of the B cell activating factor (*BAFF*) gene (rs1224141, rs12583006, rs9514828, rs1041569 and rs9514827) were evaluated in the study of Nezos *et al.* (2013), where patients with SS at high risk of developing lymphoma were characterized by higher frequency of the minor T allele of the rs9514828 and lower frequencies of the AA genotype of the rs12583006 polymorphism. The rs2230926 exonic variant of the ubiquitin-editing enzyme *TNF AIP3* that regulates nuclear factor kappa B (NF- κ B), was associated with an increased risk for lymphoma in the study of Nocturne *et al.* (2013). NF- κ B receptor upregulation has been associated with lymphoid tumorigenesis. TNF AIP3 in combination with A20 down-regulates NF- κ B activity and acts as a tumor suppressor.

Significantly lower levels of miR200b-5p, a miRNA which regulates expression of autoantibodies directed to intracellular autoantigens, La/SSB, were characterized in SS patients with MALT lymphoma compared with those without ($p < 0.05$) (Gourzi *et al.*, 2015). Similarly, in the study of Kapsogeorgou *et al.* (2018), miR200b-5p was significantly downregulated in patients with SS who would develop or had NHL, and was able to discriminate this subset ($p < 0.0001$) from those without lymphoma or those with non-SS sialadenitis. These investigators reported miR200b-5p as a strong independent predictor of

patients who would develop NHL. Regarding methylating enzymes, SS patients with lymphoma were characterized by an intense decrease of methyl CpG-binding protein 2 (MeCP2) and DNA methyltransferase (DNMT) 3B (Mavragani *et al.*, 2018). Recently, Vakrakou *et al.* (2018) reported that NLRP3 inflammasome activation and the widespread DNA accumulations in tissues, contributed a key role in NHL development in patients with SS.

v. Chemokines as biomarkers

Barone *et al.* (2008) reported that CXCL12 was principally detected in infiltrated ducts and malignant B-cells in the salivary glands of patients with SS. Additionally, CXCL12 levels were increased in MALT lymphomas and isolated tumor cells, suggesting the direct involvement of CXCL12 in the organization of ectopic reactive lymphoid tissue and its association with the malignant B-cell component and regulation of malignant B-cell survival. Similarly, Nocturne *et al.* (2015) showed that patients with SS who developed lymphoma had higher levels of serum CXCL13 (a chemokine promoting B-cell chemotaxis that promotes ectopic, B-cell rich, lymphoid tissue formation) than patients with no lymphoma (193.65 pg/ml [IQR=101.71–501.33] vs 108.31 pg/ml [IQR 59.95–197.25]; $p=0.006$) and also tended to have a higher level of serum CCL11 (139.44 pg/ml [IQR=82.91–177.73] vs 106.66 pg/ml [IQR 70.12–147.19]; $p=0.056$).

vi. Salivary biomarkers

a. Salivary proteins

Anti-coffilin-1, anti-alpha enolase, anti-Rho GDP-dissociation inhibitor 2 (RGI2) were all found to be over-expressed in patients with SS who developed MALT lymphoma compared with both patients with SS or healthy controls ($p<0.01$; $p<0.001$). The combination of these

three auto-antibodies resulted in an AUC value of 0.86 with a 75% sensitivity and 94% specificity in distinguishing SS patients with MALT lymphoma from those without MALT (Cui *et al.*, 2017).

b. Parotid scintigraphy

SS patients with class 4 involvement in the salivary glands, i.e. with severe involvement, showing no active concentration of the technetium 99 tracer, were found to have a higher rate of lymphoma development. Additionally, adjusted multivariate Cox regression analysis showed a hazard ratio (HR) of 10.51 ($p=0.002$) and Kaplan–Meier analysis showed a log-rank of 0.0005 (Ramos-Casals *et al.*, 2010).

c. Ultrasound of the major salivary glands (SGUS)

SGUS scores of 2 or 3 (Hocevar *et al.*, 2005) were associated with markers of lymphoma. Specifically, GC-like structures in the original salivary gland biopsy findings, CD4 T-cell lymphopenia, and reduced number of memory B-cells in the circulation, immunoglobulin oligo- or monoclonality in serum, the presence of salivary gland swelling, and purpura and skin vasculitis were more frequently observed in patients with SS with several or numerous or confluent rounded hypoechoic lesions compared with patients with a normal SGUS ($p<0.05$) (Theander and Mandl, 2014).

vii. Microbiological biomarkers

Only two studies assessed the potential role of microbiological biomarkers, e.g. viral or bacterial, in the prediction of lymphoma in SS patients. Higher prevalence of *Chlamydomphila psittaci* was reported in patients with SS with MALT lymphoma, compared to those with myoepithelial sialoadenitis or no lymphoproliferative disorder ($p=0.02$) (Fabris *et al.*, 2014). Hirose *et al.* (1999) reported no association between presence of Epstein-Barr virus and lymphoma development in a series of patients with SS.

5. Predictive scoring systems for development of lymphoma in salivary glands of patients with SS

A few studies (n=5) investigated possible predictive scores for lymphoma development by meaningfully combining several risk factors. Table 3 presents a comprehensive overview of these studies. The presence of hypocomplementemia, and specifically of low C4 levels, was a risk factor consistently included in all scoring systems (Baimpa *et al.*, 2009 ; Fragioudaki *et al.*, 2016 ; Ioannidis *et al.*, 2002 ; Quartuccio *et al.*, 2014; Solans-Laqué *et al.*, 2011).

Discussion

In the context of precision medicine, discovery and validation of quantifiable biomarkers defined by omics approaches, in combination with clinical phenotypic definitions associated with disease presentation, is necessary to aid in risk prediction, diagnosis, treatment outcome prediction and assessment of disease progression. Regarding SS, it is of high importance to not only predict which patients with SS are at risk of developing lymphoma, but also to predict site of emergence, since lymphomas could rise either in the salivary glands or stomach or lymph nodes or thymus. This systematic review sought to define the current state of the science relative to application of precision medicine approaches for identification, outcome prediction and management of patients with SS who are at risk for lymphoma emergence in the salivary glands, since lymphomas of the salivary glands occur with the highest frequency (Dong *et al.*, 2013), representing the vast majority of emergent lymphomas observed in SS.

Lymphoma in salivary glands of patients with SS can manifest as completely indolent, but can also be accompanied by severe disease activity, i.e. high ESSDAI, with local or more extensive dissemination. Consequently, treatment may vary from watchful waiting to more therapeutically complex approaches, such as treatment with rituximab, cyclophosphamide and prednisone (R-CP) (Pollard *et al.*, 2011). Among foci for advancement of oral precision

medicine in the context of SS, is development of the capacity to predict the development of a lymphoma in patients with SS and prognosis associated with the course of lymphoma and efficacy of treatment. Identification of appropriate biomarkers would advance achievement of these capabilities in the clinical arena. Biomarkers are defined as characteristics that can be objectively measured and evaluated as indicators of normal biological or pathogenic processes, or as indicators of pharmacologic responses to therapeutic interventions (Biomarkers Definitions Working Group, 2001). T

This systematic review delineated 57 different biomarkers in 58 studies as risk factors of lymphoma development in the salivary glands of patients with SS. These could then be further classified in: clinical and histological manifestations, serological or otherwise quantifiable through analysis in a laboratory setting, and by omics approaches including definition of genetic risks, proteomic (expression of chemokines), salivary (proteomic or metabolomic) and microbiological analyses to define potential disease-associated pathogens. The current state of the art suggests that clinical manifestations in combination with serological biomarkers currently represent the most frequently assessed variables in the clinical setting to inform delivery of personalized care, likely because of their ease of applicability. This systematic review determined that the majority of studies focused on identifying biomarkers that predict lymphoma development, while only one study assessed biomarkers predicting the progression of lymphoma (Papageorgiou *et al.*, 2015).

Conclusions of available studies regarding histological biomarkers were inconclusive. Studies with central focus on GCs reported contradictory results (Kapsogeorgou *et al.*, 2013; Johnsen *et al.*, 2014; Haacke *et al.*, 2017; Bombardieri *et al.*, 2007; Theander *et al.*, 2011; Sene *et al.*, 2018). This dichotomy could be principally attributed to the considerable variety in histological definitions of GC used in the various studies, as well as to the absence of consensus guidelines to standardize their assessment (Delli *et al.*, 2016). Biomarkers could aid in histological definition. Specifically, activation-induced deaminase, an enzyme essential for the function of GC B-cells (Bombardieri *et al.*, 2007), the long isoform of CD21 (CD21L);

a marker of follicular dendritic cells (Hillen *et al.*, 2016), and Bcl-6; a transcription factor expressed at high levels by GC B-cells (Delli *et al.*, 2017), have been proposed for definition and identification of GCs. Notably, Nakshbandi *et al.* (2019) recently showed that Bcl-6 is the most appropriate marker for identification of GCs in salivary gland biopsies of SS patients. In contrast to hematoxylin-eosin stain and CD21 immunohistochemistry, Bcl-6 supports unequivocal identification of GCs.

In one-third of the studies, patients' eligibility and recruitment method was not specified, raising concerns about possible selection bias. Additionally, in one quarter of the studies, patients were included only when data of interest were available and no additional analysis was performed to identify the impact of the missing data. Thus, it is unclear in most of the studies whether data were missing completely at random, at random or not at random. This shortcoming may have resulted in unrepresentative study populations and thus may cause bias in the validity of the biomarkers under investigation (Donders *et al.*, 2006).

Lastly, the predictive value of a biomarker, as investigated in a particular study, is applicable to the timeframe in which the recruited patients were followed (Betensky, 2015). In approximately 50% of studies, the exact follow-up period of the patients was not mentioned and the onset of lymphoma in the natural history of SS was not precisely defined. Therefore, it remains unclear how the predictive biomarker should be used in daily practice (Rector *et al.*, 2012).

Strengths and limitations

Strengths of the current systematic review were the detailed literature search on the two prevailing databases, i.e. PubMed and EMBASE, without time and language restrictions, assessment of study eligibility by two reviewers, good inter-observer agreement, and application of the QUIPS tool to assess the quality of the studies and utilization of the CHARMS checklist to extract data. The major limitation encountered in interpretation of the

outcomes was the high clinical and methodological heterogeneity of the included studies. Specifically, a variation in study populations, study designs, and outcome measures were identified which precluded meta-analysis. Lastly, the fact that studies included often patients with a mix of both salivary and extra-salivary gland lymphomas, cannot exclude the possibility that (some of) the observed predictive biomarkers are not exclusively applicable to salivary lymphomas, but could also be relevant in case of extra-salivary gland lymphomas. Since studies were included only if they reported on ≥ 5 patients with lymphoma in the salivary glands, the generalizability of the conclusions to the salivary lymphomas is, however, ensured.

Implications and future research

Future studies should comply with the QUIPS and CHARMS guidelines in order to ensure high predictive quality. Particular attention should be paid to the QUIPS domains where moderate risk of bias is observed, viz.:

- 1) the study sample should adequately represent the SS population, thus a consecutive or random sample of SS patients should be used; a case control design and inappropriate exclusion of patients should be avoided;
- 2) lymphoma should be diagnosed in a similar manner for all participants, the method used to diagnose lymphoma should be clearly defined and lymphoma should be assessed without knowledge of the candidate predictors;
- 3) important confounders should be accounted and appropriately measured;
- 4) researchers should be encouraged to develop predictive models, applying logistic regression analysis, Cox survival analysis, neural networks, or by application of machine learning techniques, whose performance and evaluation should be properly reported. In this respect, Baldini *et al.* (2018) recently showed that with artificial

neural network analyses previously hidden formation could potentially be discovered in complex diseases like SS.

The aforementioned features should be stated clearly by authors to avoid potential misinterpretation or poor evaluability. There is a need for an international prospective registry, where patients newly-diagnosed with SS according to the ACR-EULAR criteria are included with subsequent longitudinal follow-up, and collection of structured data at specifically defined time-points.

Conclusion

Rapidly expanding clinical manifestations to support definition of phenotypes and biomarkers with the potential to predict lymphoma in the salivary glands of patients with SS continue to contribute to realization of a precision medicine approach to lymphoma risk prediction in SS.

The most commonly used predictive biomarkers and clinical manifestations currently defined for use in clinical practice is documentation of low C4 levels and cryoglobulins in combination with the presence of parotid gland enlargement. The role of histological phenotypes and definition of informative biomarkers remain controversial. Increased research activity was detected with focus on defining specific genetic polymorphisms and useful clinical epigenetic markers. However, due to the high heterogeneity of studies, further research is required to elucidate the predictive value and utility of these biomarkers in a prospectively-followed SS population to evaluate their potential for translation into the clinical setting.

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Conflict of interest

The authors state that they have no conflict of interest.

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References

- Baimpa, E., Dahabreh, I.J., Voulgarelis, M., Moutsopoulos, H.M. (2009) Hematologic manifestations and predictors of lymphoma development in primary Sjögren's syndrome: Clinical and pathophysiologic aspects. *Medicine (Baltimore)*, 88:284-93. doi: 10.1097/MD.0b013e3181b76ab5
- Baldini, C., Mosca, M., Della Rossa, A., Pepe, P., Notarstefano, C., Ferro, F., Bombardieri, S. (2013). Overlap of ACA-positive systemic sclerosis and Sjögren's syndrome: a distinct clinical entity with mild organ involvement but at high risk of lymphoma. *Clin Exp Rheumatol*, 31:272-80.
- Baldini, C., Pepe, P., Luciano, N., Ferro, F., Talarico, R., Grossi, S., ... Bombardieri, S (2012). Clinical Prediction Rule for Lymphoma Development in Primary Sjögren's. *J Rheumatol*, 39:804-8. doi: 10.3899/jrheum.110754
- Baldini, C., Ferro, F., Luciano, N., Bombardieri, S., Grossi, E. (2018). Artificial neural networks help to identify disease subsets and to predict lymphoma in primary Sjögren's syndrome. *Clin Exp Rheumatol*, 36 Suppl 112:137-144.
- Barone, F., Bombardieri, M., Rosado, M.M., Morgan, P.R.,... Challacombe, S.J., De Vita, S., ... Pitzalis, C. (2008). CXCL13, CCL21, and CXCL12 expression in salivary glands of patients with Sjogren's syndrome and MALT lymphoma: association with reactive and malignant areas of lymphoid organization. *J Immunol*, 180:5130-40. doi: 10.4049/jimmunol.180.7.5130
- Betensky, R.A. (2015). Measures of follow-up in time-to-event studies: Why provide them and what should they be? *Clin Trials*, 12:403-8. doi: 10.1177/1740774515586176
- Biomarkers Definitions Working Group. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*, 69:89-95. doi: 10.1067/mcp.2001.113989

Bombardieri, M., Barone, F., Humby, F., Kelly, S., McGurk, M., Morgan, P., ... Pitzalis, C. (2007). Activation-induced cytidine deaminase expression in follicular dendritic cell networks and interfollicular large B cells supports functionality of ectopic lymphoid neogenesis in autoimmune sialoadenitis and MALT lymphoma in Sjögren's syndrome. *J Immunol*, 179:4929-38. Doi: 10.4049/jimmunol.179.7.4929

Brito-Zerón, P., Kostov, B., Fraile, G., Caravia-Durán, D., Maure, B., Rascón, F.J., ... Ramos-Casals, M.; SS Study Group GEAS-SEMI. (2017). Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. *J Hematol Oncol*, 10:90. doi: 10.1186/s13045-017-0464-5

Brito-Zerón, P., Ramos-Casals, M., Bove, A., Sentis, J., Font, J. (2007). Predicting adverse outcomes in primary Sjogren's syndrome: identification of prognostic factors. *Rheumatology (Oxford)*. 46:1359-62. doi: 10.1093/rheumatology/kem079

Carubbi, F., Alunno, A., Cipriani, P., Bartoloni, E., Baldini, C., Quartuccio, L., ... Giacomelli, R. (2015). A retrospective, multicenter study evaluating the prognostic value of minor salivary gland histology in a large cohort of patients with primary Sjögren's syndrome. *Lupus*, 24:315-20. doi: 10.1177/0961203314554251

Ciccia, F., Guggino, G., Rizzo, A., Bombardieri, M., Raimondo, S., Carubbi, F., ... Triolo, G. (2015). Interleukin (IL)-22 receptor 1 is over-expressed in primary Sjogren's syndrome and Sjögren-associated non-Hodgkin lymphomas and is regulated by IL-18. *Clin Exp Immunol*, 181:219-29. doi: 10.1111/cei.12643

Cui, L., Elzakra, N., Xu, S., Xiao, G.G., Yang, Y., Hu, S.(2017). Investigation of three potential autoantibodies in Sjogren's syndrome and associated MALT lymphoma. *Oncotarget*, 8:30039-30049. doi: 10.18632/oncotarget.15613

Delli, K., Haacke, E.A., Ihrler, S., van der Vegt, B., Vissink, A., Bootsma, H., ... Kroese, F.G. (2016). Need for consensus guidelines to standardise the assessment of germinal centres

and other histopathological parameters in salivary gland tissue of patients with primary Sjögren's syndrome. *Ann Rheum Dis*, 75:e32. doi: 10.1136/annrheumdis-2016-209480

Delli, K., Haacke, E.A., Kroese, F.G., Pollard, R.P., Ihrler, S., van der Vegt, B, ... Spijkervet, F.K. (2016). Towards personalised treatment in primary Sjögren's syndrome: baseline parotid histopathology predicts responsiveness to rituximab treatment. *Ann Rheum Dis*, 75:1933-1938. doi: 10.1136/annrheumdis-2015-208304

De Vita, S., Quartuccio, L., Salvin, S., Corazza, L., Zabotti, A., Fabris, M. (2012). Cryoglobulinaemia related to Sjogren's syndrome or HCV infection: differences based on the pattern of bone marrow involvement, lymphoma evolution and laboratory tests after parotidectomy. *Rheumatology (Oxford)*, 51:627-33. doi: 10.1093/rheumatology/ker407

Donders, A.R., van der Heijden, G.J., Stijnen, T., Moons, K.G. (2006). Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*, 59:1087-91. doi: 10.1016/j.jclinepi.2006.01.014

Dong, L., Chen, Y., Masaki, Y., Okazaki, T., Umehara, H. (2013). Possible Mechanisms of Lymphoma Development in Sjögren's Syndrome. *Curr Immunol Rev*, 9:13-22. doi: 10.2174/1573395511309010003

Fabris, M., Dolcetti, R., Pasini, E., Quartuccio, L., Pontarini, E., Salvin, S., ... De Vita, S (2014). High prevalence of Chlamydophila psittaci subclinical infection in Italian patients with Sjögren's syndrome and parotid gland marginal zone B-cell lymphoma of MALT-type. *Clin Exp Rheumatol*, 32:61-5.

Fragkioudaki, S., Mavragani, C.P., Moutsopoulos, H.M. (2016). Predicting the risk for lymphoma development in Sjogren syndrome: An easy tool for clinical use. *Medicine (Baltimore)*. 95:e3766. doi: 10.1097/MD.00000000000003766

Fragkioudaki, S., Nezos, A., Souliotis, V.L., Chatziandreu, I., Saetta, A.A., Drakoulis, N., ... Mavragani, C.P. (2017). MTHFR gene variants and non-MALT lymphoma development in primary Sjogren's syndrome. *Sci Rep.* 7:7354. doi: 10.1038/s41598-017-07347-w

Gottenberg, J.E., Seror, R., Miceli-Richard, C., Benessiano, J., Devauchelle-Pensec, V., Dieude, P., ... Mariette, X. (2013). Serum levels of beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjögren's syndrome. Data at enrollment in the prospective ASSESS cohort. *PLoS One*, 8:e59868. doi: 10.1371/journal.pone.0059868

Gourzi, V.C., Kapsogeorgou, E.K., Kyriakidis, N.C., Tzioufas, A.G. (2015). Study of microRNAs (miRNAs) that are predicted to target the autoantigens Ro/SSA and La/SSB in primary Sjögren's Syndrome. *Clin Exp Immunol.* 182:14-22. doi: 10.1111/cei.12664

Haacke, E.A., Bootsma, H., Spijkervet, F.K.L., Visser, A., Vissink, A., Kluin, P.M., Kroese, F.G.M. (2017). FcRL4+ B-cells in salivary glands of primary Sjögren's syndrome patients. *J Autoimmun.* 81:90-98. doi: 10.1016/j.jaut.2017.03.012

Haacke, E.A., van der Vegt, B., Vissink, A., Spijkervet, F.K.L., Bootsma, H., Kroese, F.G.M. (2017). Germinal centres in diagnostic labial gland biopsies of patients with primary Sjögren's syndrome are not predictive for parotid MALT lymphoma development. *Ann Rheum Dis*, 76:1781-1784. doi: 10.1136/annrheumdis-2017-211290

Hayden, J.A., van der Windt, D.A., Cartwright, J.L., Côté, P., Bombardier, C. (2013). Assessing bias in studies of prognostic factors. *Ann Intern Med*, 158:280-6. doi: 10.7326/0003-4819-158-4-201302190-00009

Hillen, M.R., Barone, F., Radstake, T.R., van Roon, J.A. (2016). Towards standardisation of histopathological assessments of germinal centres and lymphoid structures in primary Sjögren's syndrome. *Ann Rheum Dis*, 75:e31. doi: 10.1136/annrheumdis-2016-209475

Hirose, Y., Sugai, S., Masaki, Y., Ogawa, Y., Takeshita, S., Kin, C., Ogawa, N. (1999). Epstein-Barr virus study in malignant lymphoma in Sjögren's syndrome. *Int J Hematol*, 69:174-9.

Hocevar, A., Ambrozic, A., Rozman, B., Kveder, T., Tomsic, M. (2005). Ultrasonographic changes of major salivary glands in primary Sjögren's syndrome: diagnostic value of a novel scoring system. *Rheumatology (Oxford)*, 44:768–72. doi: 10.1093/rheumatology/keh588

Hodson, R. Precision medicine. (2016). *Nature*, 537:S49. doi: 10.1038/537S49a

Hood, L. & Friend, S.H. (2011). Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat Rev Clin Oncol*, 8:184-7. doi: 10.1038/nrclinonc.2010.227

Ioannidis, J.P., Vassiliou, V.A., Moutsopoulos, H.M. (2002). Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. *Arthritis Rheum*, 46:741-7. doi: 10.1002/art.10221

Ismail, F., Mahmoud, A., Abdelhaleem, H., Mamdoh, A., Geneidy, M., Kamal, E. (2013). Primary Sjögren's syndrome and B-non-Hodgkin lymphoma: role of CD4+ T lymphocytopenia. *Rheumatol Int*, 33:1021-5. doi: 10.1007/s00296-012-2464-7

Johnsen, S.J., Berget, E., Jonsson, M.V., Helgeland, L., Omdal, R., Jonsson, R. (2014). Evaluation of germinal center-like structures and B cell clonality in patients with primary Sjögren syndrome with and without lymphoma. *J Rheumatol*, 41:2214-22. doi: 10.3899/jrheum.131527

Johnsen, S.J., Gudlaugsson, E., Skaland, I., Janssen, E.A., Jonsson, M.V., Helgeland, L., ... Jonsson, R., Omdal, R. (2016). Low Protein A20 in Minor Salivary Glands is Associated with Lymphoma in Primary Sjögren's Syndrome. *Scand J Immunol*, 83:181-7. doi: 10.1111/sji.12405

Kapsogeorgou, E.K., Christodoulou, M.I., Panagiotakos, D.B., Paikos, S., Tassidou, A., Tzioufas, A.G., Moutsopoulos, (2013). H.M. Minor salivary gland inflammatory lesions in Sjögren syndrome: do they evolve? *J Rheumatol*, 40:1566-71. doi: 10.3899/jrheum.130256

Kapsogeorgou, E.K., Papageorgiou, A., Protogerou, A.D., Voulgarelis, M., Tzioufas, A.G. (2018). Low miR200b-5p levels in minor salivary glands: a novel molecular marker predicting lymphoma development in patients with Sjögren's syndrome. *Ann Rheum Dis*, 77:1200-1207. doi: 10.1136/annrheumdis-2017-212639

Kimman, J., Bossuyt, X., Blockmans, D. (2018). Prognostic value of cryoglobulins, protein electrophoresis, and serum immunoglobulins for lymphoma development in patients with Sjögren's syndrome. A retrospective cohort study. *Acta Clin Belg*, 73:169-181. doi: 10.1080/17843286.2017.1373966

Kroese, F.G.M. and Bootsma, H. (2013). Biomarkers: New biomarkers for Sjogren's Syndrome- time to treat patients. *Nat Rev Rheumatol*, 9:570-572. doi: 10.1038/nrrheum.2013.143

Kruger, K., Binder, C. (1998). Risk indicators for malignant degeneration of Sjogren's syndrome. *Akt. Rheumtol*, 23:100-106.

Martel, C., Gondran, G., Launay, D., Lalloué, F., Palat, S., Lambert, M., ... Fauchais, A.L.(2011). Active immunological profile is associated with systemic Sjögren's syndrome. *J Clin Immunol*, 31:840-7. doi: 10.1007/s10875-011-9553-3

Mavragani, C.P., Nezos, A., Sagalovskiy, I., Seshan, S., Kirou, K.A., Crow, M.K. (2018). Defective regulation of L1 endogenous retroelements in primary Sjogren's syndrome and systemic lupus erythematosus: Role of methylating enzymes. *J Autoimmun*, 88:75-82. doi: 10.1016/j.jaut.2017.10.004

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G.; PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*, 339:b2535. doi: 10.1136/bmj.b2535

Moons, K.G., de Groot, J.A., Bouwmeester, W., Vergouwe, Y., Mallett, S., Altman, D.G., ... Collins, G.S. (2014). Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med*, 11(10):e1001744. doi: 10.1371/journal.pmed.1001744

Nakshbandi, U., Haacke, E.A., Bootsma, H., Spijkervet, F.K.L., Vissink, A., van der Vegt, B., Kroese, F.G.M. (2019). Bcl6 is the most appropriate marker for identification of germinal centres in salivary gland biopsies of primary Sjögren's Syndrome patients. *Rheumatology* (2019, in press).

Nezos, A., Papageorgiou, A., Fragoulis, G., Ioakeimidis, D., Koutsilieris, M., Tzioufas, A.G., ... Mavragani, C.P. (2014). B-cell activating factor genetic variants in lymphomagenesis associated with primary Sjogren's syndrome. *J Autoimmun*, 51:89-98. doi: 10.1016/j.jaut.2013.04.005

Nocturne, G., Boudaoud, S., Miceli-Richard, C., Viengchareun, S., Lazure, T., Nititham, J., ... Mariette, X. (2013). Germline and somatic genetic variations of TNFAIP3 in lymphoma complicating primary Sjogren's syndrome. *Blood*, 122:4068-76. doi: 10.1182/blood-2013-05-503383

Nocturne, G., Seror, R., Fogel, O., Belkhir, R., Boudaoud, S., Saraux, A., ... Mariette, X. (2015). CXCL13 and CCL11 Serum Levels and Lymphoma and Disease Activity in Primary Sjögren's Syndrome. *Arthritis Rheumatol*, 67:3226-33. doi: 10.1002/art.39315

Nocturne, G., Virone, A., Ng, W.F., Le Guern, V., Hachulla, E., Cornec, D., ... Mariette, X. (2016). Rheumatoid Factor and Disease Activity Are Independent Predictors of Lymphoma in Primary Sjögren's Syndrome. *Arthritis Rheumatol*, 68:977-85. doi: 10.1002/art.39518

Papageorgiou, A., Ziogas, D.C., Mavragani, C.P., Zintzaras, E., Tzioufas, A.G., Moutsopoulos, H.M., Voulgarelis, M. (2015). Predicting the outcome of Sjogren's syndrome-associated non-hodgkin's lymphoma patients. *PLoS One*, 10:e0116189. doi: 10.1371/journal.pone.0116189

Pollard, R.P., Pijpe, J., Bootsma, H., Spijkervet, F.K., Kluin, P.M., Roodenburg, J.L., ...van Imhoff, G.W. (2011). Treatment of mucosa-associated lymphoid tissue lymphoma in Sjogren's syndrome: a retrospective clinical study. *J Rheumatol*, 38:2198-208. doi: 10.3899/jrheum.110077

Qin, B., Wang, J., Yang, Z., Yang, M., Ma, N., Huang, F., Zhong, R. (2015). Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis*, 74: 1983-1989. doi: 10.1136/annrheumdis-2014-205375

Quartuccio, L., Baldini, C., Bartoloni, E., Priori, R., Carubbi, F., Corazza, L., ... De Vita, S. (2015). Anti-SSA/SSB-negative Sjögren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution. *Autoimmun Rev*, 14:1019-22. doi: 10.1016/j.autrev.2015.07.002

Quartuccio, L., Isola, M., Baldini, C., Priori, R., Bartoloni Bocci, E., Carubbi, F., ... De Vita, S. (2014). Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. *J Autoimmun*, 51:75-80. doi: 10.1016/j.jaut.2013.10.002

Quartuccio, L., Salvin, S., Fabris, M., Maset, M., Pontarini, E., Isola, M., De Vita, S. (2013). BLYS upregulation in Sjogren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal expansion in the salivary glands. *Rheumatology (Oxford)*, 52:276-81. doi: 10.1093/rheumatology/kes180

Ramos-Casals, M., Brito-Zerón, P., Perez-DE-Lis, M., Diaz-Lagares, C., Bove, A., Soto, M.J., ... Pons, F. (2010). Clinical and prognostic significance of parotid scintigraphy in 405

patients with primary Sjogren's syndrome. *J Rheumatol.* 37:585-90. doi: 10.3899/jrheum.090835

Ramos-Casals, M., Brito-Zerón, P., Yagüe, J., Akasbi, M., Bautista, R., Ruano, M., ... Font. J. (2005). Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjogren's syndrome. *Rheumatology (Oxford)*, 44:89-94. doi: 10.1093/rheumatology/keh407

Ramos-Casals, M., Solans, R., Rosas, J., Camps, M.T., Gil, A., Del Pino-Montes, ... Pallarés, L.; GEMESS Study Group. (2008). Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine (Baltimore)*, 87(4):210-9. doi: 10.1097/MD.0b013e318181e6af

Rector, T.S., Taylor, B.C., Wilt, T.J. (2012). Chapter 12: systematic review of prognostic tests. *J Gen Intern Med*, Suppl 1:S94-101. doi: 10.1007/s11606-011-1899-y

Retamozo, S., Gheitasi, H., Quartuccio, L., Kostov, B., Corazza, L., Bové, A., ... Brito-Zerón, P. (2016). Cryoglobulinaemic vasculitis at diagnosis predicts mortality in primary Sjögren syndrome: analysis of 515 patients. *Rheumatology (Oxford)*, 55:1443-51. doi: 10.1093/rheumatology/kew194

Risselada, A.P., Hair, M.D. Kruize, A.A., Bijlsma, J.W., van Roon, J.A. (2015). Lymphocytic focus score as a prognostic tool. *Ann Rheum Dis*, 74(4):e31. doi: 10.1136/annrheumdis-2014-207150

Risselada, A.P., Kruize, A.A., Bijlsma, J.W. (2013). Clinical features distinguishing lymphoma development in primary Sjögren's Syndrome--a retrospective cohort study. *Semin Arthritis Rheum*, 43:171-7. doi: 10.1016/j.semarthrit.2013.03.001

Risselada, A.P., Kruize, A.A., Goldschmeding, R., Lafeber, F.P., Bijlsma, J.W., van Roon, J.A. (2014). The prognostic value of routinely performed minor salivary gland assessments

in primary Sjögren's syndrome. *Ann Rheum Dis*, 73:1537-40. doi: 10.1136/annrheumdis-2013-204634

Sène, D., Ismael, S., Forien, M., Charlotte, F., Kaci, R., Cacoub, P., ... Lioté, F. (2018). Ectopic germinal centres in labial minor salivary glands and male gender are additional risk factors for non-Hodgkin's lymphoma in primary Sjögren's syndrome. *Arthritis Rheumatol*. [Epub ahead of print]. doi: 10.1002/art.40714

Shiboski, C.H., Shiboski, S.C., Seror, R., Criswell, L.A., Labetoulle, M., Lietman, T.M., ... Mariette, X.; International Sjögren's Syndrome Criteria Working Group. (2017). 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis*, 76:9-16. doi: 10.1136/annrheumdis-2016-210571

Solans-Laqué, R., López-Hernandez, A., Bosch-Gil, J.A., Palacios, A., Campillo, M., Vilardell-Tarres, M.(2011). Risk, predictors, and clinical characteristics of lymphoma development in primary Sjögren's syndrome. *Semin Arthritis Rheum*, 41:415-23. doi: 10.1016/j.semarthrit.2011.04.006

Sugai, S., Saito, I., Masaki, Y., Takeshita, S., Shimizu, S., Tachibana, J., Miyasaka, N. (1994). Rearrangement of the rheumatoid factor-related germline gene Vg and bcl-2 expression in lymphoproliferative disorders in patients with Sjögren's syndrome. *Clin Immunol Immunopathol*, 72(2):181-6.

Sutcliffe, N., Inanc, M., Speight, P., Isenberg, D. (1998). Predictors of lymphoma development in primary Sjögren's syndrome. *Semin Arthritis Rheum*, 28:80-7.

Theander, E., Henriksson, G., Ljungberg, O., Mandl, T., Manthorpe, R., Jacobsson, L.T. (2006). Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on

cancer incidence and lymphoma predictors. *Ann Rheum Dis*, 65:796-803. doi: 10.1136/ard.2005.041186

Theander, E., Mandl, T. (2014). Primary Sjögren's syndrome: diagnostic and prognostic value of salivary gland ultrasonography using a simplified scoring system. *Arthritis Care Res (Hoboken)*, 66:1102-7. doi: 10.1002/acr.22264

Theander, E., Vasaitis, L., Baecklund, E., Nordmark, G., Warfvinge, G., Liedholm, R., ...Jonsson, M.V. (2011). Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. *Ann Rheum Dis*, 70:1363-8. doi: 10.1136/ard.2010.144782

Tobón, G.J., Renaudineau, Y., Hillion, S., Cornec, D., Devauchelle-Pensec, V., Youinou, P., Pers, J.O. (2010). The Fms-like tyrosine kinase 3 ligand, a mediator of B cell survival, is also a marker of lymphoma in primary Sjögren's syndrome. *Arthritis Rheum*, 62:3447-56. doi: 10.1002/art.27611

Tzioufas, A.G., Boumba, D.S., Skopouli, F.N., Moutsopoulos, H.M. (1996). Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjögren's syndrome. *Arthritis Rheum*, 39:767-72.

Ussmüller, J., Reinecke, T., Donath, K., Jaehne, M. (2002). Chronic myoepithelial sialadenitis - symptomatology, clinical signs, differential diagnostics. *Laryngorhinootologie*, 81:111-7. doi: 10.1055/s-2002-23111

Vakrakou, A.G., Boiu, S., Ziakas, P.D., Xingi, E., Boleti, H., Manoussakis, M.N. (2018). Systemic activation of NLRP3 inflammasome in patients with severe primary Sjögren's syndrome fueled by inflammagenic DNA accumulations. *J Autoimmun*, 91:23-33. doi: 10.1016/j.jaut.2018.02.010

Vissink, A., Bootsma, H., Spijkervet, F.K., Wong, D.T., Kallenberg, C.G. (2012). Current and future challenges in primary Sjögren's syndrome. *Curr Pharm Biotechnol*, 13:2026-2045.

Vitali, C., Bombardieri, S., Jonsson, R., Moutsopoulos, H.M., Alexander, E.L., Carsons, S.E., ... Weisman, M.H.; European Study Group on Classification Criteria for Sjögren's Syndrome. (2002). Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*, 61:554-8.

Vitali, C., Bombardieri, S., Moutsopoulos, H.M., Balestrieri, G., Bencivelli, W., Bernstein, R.M., ... Youinou, P. (1993). Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum*, 36:340-7.

Voulgarelis, M., Dafni, U.G., Isenberg, D.A., Moutsopoulos, H.M. (1999). Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. *Arthritis Rheum*, 42:1765-72. doi: 10.1002/1529-0131(199908)42:8<1765::AID-ANR28>3.0.CO;2-V

Voulgarelis, M., Ziakas, P.D., Papageorgiou, A., Baimpa, E., Tzioufas, A.G., Moutsopoulos, H.M. (2012). Prognosis and outcome of non-Hodgkin lymphoma in primary Sjögren syndrome. *Medicine (Baltimore)*, 91:1-9. doi: 10.1097/MD.0b013e31824125e4

Tables:

Table 1: Overview of studies assessing the predictive value of clinical manifestations *in combination with* serological biomarkers.

Authors, year	Participants	Biomarker(s)	Conclusion
Baimpa <i>et al.</i> , 2009	<ul style="list-style-type: none"> 536 SS 	<ul style="list-style-type: none"> Cryoglobulinemia Low C4 levels Lymphadenopathy Neutropenia Splenomegaly 	<ul style="list-style-type: none"> Neutropenia (HR, 8.97; 95% CI, 1.10-73.30; p=0.04), cryoglobulinemia (HR, 2.91; 95% CI, 1.15-6.44; p=0.008), splenomegaly (HR, 3.97; 95% CI, 1.49-10.62; p=0.006), lymphadenopathy (HR, 2.62; 95% CI, 1.15-5.94; p=0.021), and low C4 levels (HR, 3.31; 95% CI, 1.35-8.12; p=0.009) were independent risk factors for the development of lymphoma. Patients carrying any of these factors had a more than 5.4-fold increased risk of NHL compared to patients with no risk factors.
Baldini <i>et al.</i> , 2013	<ul style="list-style-type: none"> 387 SS 102 anti-centromere (ACA) positive systemic sclerosis (SSc) 81 sicca SSc 41 overlap (SS and SSc) 	<ul style="list-style-type: none"> Hypergammaglobulinaemia Leukocytopenia Parotid enlargement Purpura Peripheral nervous system involvement 	<ul style="list-style-type: none"> Parotid enlargement, purpura, peripheral nervous system involvement, hypergammaglobulinaemia and leukocytopenia were significant risk factors for non-Hodgkin's lymphoma (p<0.008) in SS patients.
Fragioudaki <i>et al.</i> , 2016	<ul style="list-style-type: none"> 381 SS without NHL 73 SS with MALT 19 SS with (non-MALT) NHL 	<ul style="list-style-type: none"> Anti-Ro/SS Anti-La/SSB positivity Low C4 levels Lymphadenopathy Monoclonal gammopathy Parotid enlargement Raynaud phenomenon 	<ul style="list-style-type: none"> Salivary gland enlargement (OR 4.3, 95% 2.0–9.1), lymphadenopathy (OR 4.2, 95% 1.8–9.9), Raynaud phenomenon (OR 2.3, 95% 1.0–5.2), anti-Ro/SS or/and anti-La/SSB positivity (OR 3.8, 95% 1.1–13.4), RF positivity (OR 3.7, 95% 1.4–10.0), monoclonal gammopathy (OR 3.2, 95% 1.0–9.8), and C4 hypocomplementemia (OR 3.0, 95% 1.3–6.8) were identified as independent predictors for NHL development. The ORs, 95% CIs and p-values for NHL

			<p>development in the presence of:</p> <ol style="list-style-type: none"> all 7 risk factors were 210.0 (10.0–4412.9), $p < 0.0001$ compared to those with 2 or less risk factors. 3 to 6 risk factors were 16.6 (6.5–42.5), $p < 0.05$ in comparison with patients presenting with 2 or less risk factors.
Ioannidis <i>et al.</i> , 2002	<ul style="list-style-type: none"> 723 SS patients 	<ul style="list-style-type: none"> Low C4 levels Parotid enlargement Purpura (palpable) 	<ul style="list-style-type: none"> Parotid enlargement (HR 5.21, 95% CI 1.76–15.4; $p = 0.003$), palpable purpura (HR 4.16, 95% CI 1.65–10.5; $p = 0.002$), and low C4 levels (HR 2.40, 95% CI 0.99–5.83; $p = 0.052$) were independent predictors of lymphoma or other lymphoproliferative disease. Patients with at least 1 of these 3 adverse risk factors at baseline had a 9.08-fold higher risk of developing lymphoma or other lymphoproliferative disease in the future (95% CI 2.13–38.7) than those who did not.
Ismail <i>et al.</i> , 2013	<ul style="list-style-type: none"> PART I: 8 SS patients with B-cell NHL PART II: - 50 SS - 25 healthy 	<ul style="list-style-type: none"> Cryoglobulin positivity Fibromyalgia High lactic dehydrogenase (LDH) Low C3 and C4 levels Lymphadenopathy Lymphocytopenia (CD4+) Parotid enlargement Purpura 	<ul style="list-style-type: none"> Significant difference was observed between SS patients with lymphoma and those without lymphoma in the prevalence of parotid enlargement, lymphadenopathy, purpura, fibromyalgia, low C3 and C4, cryoglobulin positivity, and high lactic dehydrogenase (LDH) and CD4+ lymphocytopenia ($p < 0.05$).
Kruger & Binder, 1998	<ul style="list-style-type: none"> 248 SS 	<ul style="list-style-type: none"> Anti-SSA Cryoglobulinaemia Hypergammaglobulinaemia Leukopenia, Neurological involvement Parotid enlargement 	<ul style="list-style-type: none"> Significant difference between SS patients with lymphoma and those without lymphoma in the prevalence of parotid enlargement, vasculitis, splenomegaly, neurological involvement, hypergammaglobulinemia, cryoglobulinemia, leukopenia, high titre RF, SSA were significantly

		<ul style="list-style-type: none"> • RF (high titre) • Splenomegaly • Vasculitis 	correlated with the occurrence of lymphoma (p<0.05).
Nocturne <i>et al.</i> , 2016	<ul style="list-style-type: none"> • PART I: 101 SS patients with lymphoma • PART II: <ul style="list-style-type: none"> - 77 SS patients with lymphoma - 154 SS patients without lymphoma 	<ul style="list-style-type: none"> • ClinESSDAI score ≥ 5 • Cryoglobulinemia • ESSDAI • low C4 level • lymphopenia • Parotid enlargement • RF 	<ul style="list-style-type: none"> • Model 1: independently associated with development of lymphoma in patients with primary SS were salivary gland enlargement (OR 3.48 95% CI 1.50–8.07; p=0.0037), presence of RF (OR 3.04 1. 95%CI 33–6.93; p=0.0083), presence of cryoglobulinemia (OR 3.68 95% CI 1.38–9.83; p=0.0093), low C4 level (OR 3.16 95%CI 1.32–7.55; p=0.0098), and lymphopenia (OR 5.65 95% CI 2.46–12.99; p=0.0001) • Model 2: independently associated with development of lymphoma were ESSDAI (OR 3.84, 95% CI 1.98–7.43; p=0.0001) and RF (OR 3.40 [95% CI 1.71–6.75; =0.0005) • Model 3: independently associated with the development of lymphoma were RF positivity (OR 4.01, 95% CI 1.78–9.00; p=0.0008), presence of cryoglobulinemia (OR 4.07, 95% CI 1.65–10.02; p=0.0023), low C4 (OR 2.33 95% CI 1.05–5.15; p=0.0372) and ClinESSDAI score ≥ 5 (OR 3.53 95% CI 1.63–7.65; p=0.0014) were independently associated with the development of lymphoma.
Papageorgiou <i>et al.</i> , 2015	<ul style="list-style-type: none"> • 77 SS patients with lymphoma 	<ul style="list-style-type: none"> • Total ESSDAI score >10 • International prognostic index (IPI) 	<ul style="list-style-type: none"> • SS patients with lymphoma and high disease activity (total ESSDAI score >10) had greater risk to experience a death (OR=5.241, 95% CI: 1.034–26.568, p=0.045) or an event, i.e. lymphoma relapse, treatment failure, disease progression, histological transformation, (OR=4.317, 95% CI: 1.146–9.699, p=0.008), and significantly worse event free survival (EFS) and overall survival compared to SS patients with lymphoma and low total ESSDAI (score 10) (EFS: log-rank p=0.001,

			<p>HR=4.541, 95% CI: 1.772–11.637; OS: log-rank $p=0.011$, HR=5.946, 95% CI: 1.259–28.077).</p> <ul style="list-style-type: none"> Improvement in the total ESSDAI score six months after completion of first-line treatment (delta ESSDAI) among patients who had experienced an event (mean delta ESSDAI\pmSD: 4.59\pm1.68) was significantly less than that seen in event-free patients (mean delta ESSDAI\pmSD: 6.87\pm3.33) ($p=0.005$). In high/high-intermediate international prognostic index (IPI) group of patients, the risk of death was 13.867 times greater (95% CI: 2.656–72.387, $p=0.002$) and the risk of event was 12.589 times greater (95% CI: 3.911–40.526, $p<0.001$) compared to low/low-intermediate IPI risk group. SS-associated NHL patients with bone marrow involvement at lymphoma diagnosis had 3.333 times greater risk (95% CI: 1.146–9.699, $p=0.027$) to experience an event during follow-up.
Risselada <i>et al.</i> , 2013	<ul style="list-style-type: none"> 195 SS patients 	<ul style="list-style-type: none"> ESSDAI Low C4 levels Parotid gland enlargement 	<ul style="list-style-type: none"> Parotid gland enlargement (OR 2.84) and low C4 (OR 7.71) were observed more commonly in SS patients developing NHL. Presence of IgM kappa clonal components was associated with lymphoma in 64% of cases. Disease activity (ESSDAI)/severity (cumulative ESSDAI and extraglandular manifestation) scores at first visit could not predict lymphoma development, nor was the pSS disease course significantly worse in patients with NHL.
Solans-Laqué <i>et al.</i> , 2011	<ul style="list-style-type: none"> 115 SS patients 	<ul style="list-style-type: none"> Anemia Hypergammaglobulinemia Leukopenia Low C3 levels 	<ul style="list-style-type: none"> Univariate Cox regression analysis identified parotid enlargement (HR 6.75, 95% CI 1.89-23.99), palpable purpura (HR 8.04, 95% CI 2.33-27.67), anemia (HR 3.43, 95% CI 1.04-11.35), leukopenia

		<ul style="list-style-type: none"> • Low C4 levels • Parotid enlargement • Purpura (palpable) 	<p>(HR 8.70, 95% CI 2.38-31.82), lymphocytopenia (HR 16.47, 95% CI 3.45-78.76), hypergammaglobulinemia (HR 4.06, 95% CI 1.06-15.58), low C4 levels (HR 39.70, 95% CI 8.85-126.18), and low C3 levels (HR 36.65, 95% CI 10.65- 116.12) at the time of pSS diagnosis, as significant predictors of lymphoproliferative disease.</p> <ul style="list-style-type: none"> • The multivariate analysis identified only lymphocytopenia and low C3/C4 levels at pSS diagnosis as independent predictors of lymphoma.
Voulgarelis <i>et al.</i> , 1999	<ul style="list-style-type: none"> • 33 SS patients with NHL 	<ul style="list-style-type: none"> • Anemia • Low grade fever • Lymphadenopathy • Lymphopenia • Peripheral nerve involvement • Vasculitis 	<ul style="list-style-type: none"> • Lymphadenopathy (65.6%), skin vasculitis (33.3%), peripheral nerve involvement (24.2%), low grade fever (25%), anemia (48.1%) and lymphopenia (78.6%) were significantly more frequently observed in SS patients who developed a lymphoma than the general SS population.

Table 2: Overview of studies assessing the predictive role of serological biomarkers alone.

Authors, year	Participants	Biomarker(s)	Conclusion
Brito-Zeron <i>et al.</i> , 2017	<ul style="list-style-type: none">1300 SS patients	<ul style="list-style-type: none">AnemiaCryoglobulinemiaHypergammaglobulenemiaLow C3 levelsLow C4 levels	<ul style="list-style-type: none">For MALT lymphomas, baseline prognostic factors associated with B-cell MALT lymphomas were cryoglobulins (HR 6.32; $p < 0.001$) and low C3 levels (HR 3.25; $p=0.010$)For B-cell non- MALT lymphomas, the prognostic factors included anemia (HR 2.58; $p=0.047$), monoclonal gammopathy (HR 3.45; $p=0.024$), cryoglobulins (HR 3.34; $p=0.028$), and low C4 levels (HR 3.83; $p=0.014$).
De Vita <i>et al.</i> , 2012	<ul style="list-style-type: none">41 SS patients with parotid myoepithelial sialadenitis or B-cell NHL	<ul style="list-style-type: none">Cryoglobulinemia	<ul style="list-style-type: none">Significantly higher prevalence of cryoglobulinemia in SS patients with lymphoma (72.2%) than in SS patients with parotid myoepithelial sialadenitis (72.2% vs 30.4%, $p=0.01$).
Kimman <i>et al.</i> , 2018	<ul style="list-style-type: none">180 SS patients	<ul style="list-style-type: none">CryoglobulinaemiaGammaglobulinsIgGIgMLow C3 levelsMonoclonal bands on protein electrophoresisHypocomplementemia	<ul style="list-style-type: none">Cryoglobulins were significantly higher in lymphoma patients compared to non-lymphoma patients (121 ± 250 versus 8 ± 24.9 mg/L for IgG; 231 ± 422 versus 13 ± 30 mg/L for IgM; 10 ± 20 versus 1 ± 4 mg/L for IgA in the cryoprecipitate).Cryoglobulin levels were significantly more increasing (p-values for IgG=0.0007; for IgM=0.0123; and for IgA in the cryoprecipitate <0.0001) in the time period before the lymphoma diagnosis in lymphoma patients compared to non-lymphoma patients

			<ul style="list-style-type: none"> Low C3 (OR 13.9) or C4 (OR 7.1) levels, a decreasing total complement activity (OR 6.6), decreasing gammaglobulins (OR 13.4), a persistent detection of monoclonal bands (OR 14.6) on protein electrophoresis, a low or decreasing serum IgG (OR 18), and decreasing IgM-serum levels (OR 17.7) were significantly associated with lymphoma.
Martel <i>et al.</i> , 2011	<ul style="list-style-type: none"> 445 SS patients 	<ul style="list-style-type: none"> Cryoglobulinemia 	<ul style="list-style-type: none"> 9% of SS patients with cryoglobulinemia vs 3% of SS patients without cryoglobulinemia developed lymphoma ($p < 0.05$).
Quartuccio <i>et al.</i> , 2015	<ul style="list-style-type: none"> 548 SS patients 	<ul style="list-style-type: none"> Anti-SSA Anti-SSB Positive histology 	<ul style="list-style-type: none"> SS patients with a positive histology and SSA/SSB positivity developed lymphoma more frequently compared to the ones with only positive histology (6.4 vs 0.9%, $p = 0.002$) and absence of SSA/SSB.
Quartuccio <i>et al.</i> , 2014	<ul style="list-style-type: none"> 40 SS patients with NHL 17 SS patients with cryoglobulinemic vasculitis 180 SS patients with salivary gland swelling 424 SS patients without NHL or prelymphomatous conditions 	<ul style="list-style-type: none"> Anti-SSB Cryoglobulinemia Leukopenia Low C4 	<ul style="list-style-type: none"> Positive serum cryoglobulins [relative-risk ratio (RRR) 6.8, 95% CI 2.1-22.1], low C4 (RRR 8.3, 95% CI 3.6-19.2), anti-La (RRR 5.2, 95% CI 2.3-11.9), and leukopenia (RRR 3.3, 95% CI 1.5-7.05) were the selected variables, by multinomial logistic analyses, that distinguished SS patients with NHL from control group. A score 2 (i.e., the positivity of at least 2 biomarkers), showed a sensitivity for

			lymphoma of 71.8% (CI 55.1-85.0) and specificity of 79.0% (CI 72.1-84.9).
Ramos-Casals <i>et al.</i> , 2005	<ul style="list-style-type: none"> 336 patients with SS 	<ul style="list-style-type: none"> Low C3 levels Low C4 levels 	<ul style="list-style-type: none"> SS patients with low C4 levels showed a higher prevalence of lymphoma (10 vs 2%, p=0.013); SS patients with low C3 levels showed a higher prevalence of lymphoma (10 vs 2%, p=0.017).
Ramos-Casals <i>et al.</i> , 2008	<ul style="list-style-type: none"> 1010 patients with SS 	<ul style="list-style-type: none"> Hypocomplemetemia 	<ul style="list-style-type: none"> SS patients with hypocomplemetemia had a higher frequency of lymphoma (p=0.01).
Retamozo <i>et al.</i> , 2016	<ul style="list-style-type: none"> 515 patients with SS 	<ul style="list-style-type: none"> Cryoglobulinemia Vasculitis (cryoglobulinemic) 	<ul style="list-style-type: none"> Compared with patients without cryoglobulins, patients with cryoglobulins who fulfilled [hazard ratio (HR)=7.47, 95% CI: 3.38, 16.53] and did not fulfil (HR=2.56, 95% CI: 1.03, 6.35) cryoglobulinemic vasculitis criteria both showed a higher risk of B-cell lymphoma in the univariate analysis, but not in the multivariate models.
Tobon <i>et al.</i> , 2013	<ul style="list-style-type: none"> 369 patients with SS 50 healthy controls 	<ul style="list-style-type: none"> Fms-like tyrosine kinase 3 ligand 	<ul style="list-style-type: none"> Higher levels of Fms-like tyrosine kinase 3 ligand were significantly associated with a history of lymphoma (p=0.0001) in SS patients.

Tzioufas <i>et al.</i> , 1996	<ul style="list-style-type: none"> 103 patients with SS 	<ul style="list-style-type: none"> Cryoglobulinemia 	<ul style="list-style-type: none"> Cryoglobulinemia was found as the predominant factor ($r=0.421$, $p=0.0009$) for lymphoma development.
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Table 3: Scoring systems for predicting lymphoma development in the salivary glands of patients with SS.

Authors, year	Risk factors	Prognostic classification	Probability or risk of developing lymphoma per group
Baimpa <i>et al.</i> , 2009	1. Cryoglobulinemia 2. Low C4 levels 3. Neutropenia 4. Splenomegaly	Group A: Low risk if presence of 0 risk factors Group B: High risk if presence of ≥ 1 risk factors	Group A: 3.6% probability Group B: 20.6% probability
Fragioudaki <i>et al.</i> , 2016	1. Anti-Ro/SS 2. Anti-La/SSB positivity 3. Low C4 levels 4. Lymphadenopathy 5. Monoclonal gammopathy 6. Parotid enlargement 7. Raynaud's phenomenon	Group A: presence of ≤ 2 risk factors Group B: presence of 3-6 risk factors Group C: presence of all 7 risk factors	Group A: 3.8% probability Group B: 39.9% probability Group C: 100% probability
Ioannidis <i>et al.</i> , 2002	1. Low C4 levels 2. Palpable purpura 3. Parotid enlargement	Group A: Low risk if presence of 0 risk factors Group B: High risk if presence of ≥ 1 risk factors	Group A: reference group Group B: 9.08-fold higher risk than Group A
Quartuccio <i>et al.</i> , 2014	1. Anti-SSB 2. Cryoglobulinemia 3. Leukopenia 4. Low C4 levels	Group A: Presence of < 2 risk factors Group B: presence of ≥ 2 risk factors	Group A: reference group Group B: 10-fold risk than Group A
Solans-Laque <i>et al.</i> , 2011	1. Lymphocytopenia 2. Hypocomplementemia	Group A: Low risk if presence of 0 risk factors Group B: High risk if presence of ≥ 1 risk factors	Group A: reference group Group B: significantly higher risk than Group A (no exact numbers are given)



